

## **REMARKS**

### **Formalities**

Claims 42-46 have been canceled. Claims 36 and 47 have been amended. The amendments to the claims do not add or constitute new matter. Support for the amendments may be found throughout the specification and originally filed claims. More particularly, support for the amendments may be found, for example, at page 9, line 1 through page 15, line 20, and at page 51, line 25 through page 54, line 15, of the specification. As such, no new matter has been added.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 36-41 and 47-48 are pending in the instant application.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

### **Rejection under 35 U.S.C. § 101**

The Examiner has rejected claims 36-48 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicants respectfully traverse the rejection. Claims 42-46 have been canceled. Applicants believe the rejection has been overcome in light of the arguments presented below.

Claims 36-41 and 47-48 are drawn to a transgenic mouse whose genome comprises a homozygous disruption in the mouse glucocorticoid induced receptor gene, which results in several detectable and useful phenotypes. These phenotypes include hyperactivity, reduced anxiety, decreased propensity toward behavioral despair and decreased propensity toward depression, when compared to control wild-type mice. These phenotypes were determined in standard behavioral tests, using uniform procedures commonly used to determine behavioral phenotypes of transgenic animals.

Applicants submit that in order to satisfy the utility requirements set forth in 35 U.S.C. § 101, the specification must assert a specific and substantial utility that is credible to a skilled artisan, or the utility of the claimed invention must be apparent to the skilled artisan. See MPEP § 2107. Applicants believe that these requirements have been satisfied by the demonstration of a phenotype(s) exhibited by the transgenic mouse as described in the instant specification. More particularly, the claimed transgenic mouse exhibits several phenotypes resulting from disruption of the glucocorticoid induced receptor gene described in the specification, including hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression, making the transgenic mouse a model for conditions or disorders related to these phenotypes, such as hyperactivity, anxiety or depression. As such, the transgenic mouse could be used to identify, investigate or develop treatments capable of modifying or ameliorating these conditions or phenotypes caused by disruption of the specific glucocorticoid-induced receptor gene in the transgenic mouse by the present invention. This utility for the transgenic mouse was asserted in the instant specification (see, *e.g.*, page 3, lines 8-23 and page 17, lines 12-26, of the specification). Such a utility is specific to the claimed mouse because it is specific to the phenotype(s) exhibited by the mouse as a result of the disruption.

Furthermore, the asserted utility for the transgenic mouse is substantial and credible to the skilled artisan. A person of skill in the art would recognize and value the transgenic mouse as a tool for investigating treatments, such as therapeutic compounds, capable of modulating or ameliorating the conditions or phenotypes resulting from the disruption as claimed. The utility of transgenic knockout animals, and in particular knockout mice, is well recognized in the art, and it is generally accepted that such transgenic knockout mice represent a valuable method for determining the function of genes. In the present case, Applicants' disclosure related to the phenotypes of the transgenic mice has established that this gene plays a role in conditions or disorders related to activity or hyperactivity, anxiety and/or depression, as noted above. The value of such an *in vivo* model for these conditions would be immediately apparent to a person skilled in the art, in light of the homology between the mouse and human genomes, and the general acceptance that gene function in the mouse is related to and representative of that of humans. This is evidenced by the trend in the art to produce transgenic animals or mice with disruptions in all genes.

The Examiner has based the rejection on an alleged lack of correlation between disruption of the glucocorticoid-induced receptor gene, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression and any disease or disorder. Applicants are not aware of any requirement for such a correlation in order to establish the utility of transgenic mice, particularly when the transgenic mice exhibit a phenotype, such as the claimed transgenic mice. Applicants submit that the asserted utility of investigating methods or treatments, such as therapeutic compounds, capable of modulating the phenotypes exhibited as a result of the claimed disruption is sufficient to satisfy the utility requirements. Applicants do not believe that the disruption or the phenotype is required to be linked to a “disease or disorder” for it to be a useful phenotype. Despite this, Applicants submit that the specification has demonstrated that the disruption and the resulting phenotypes are linked to one or more diseases or disorders, specifically hyperactivity, anxiety and depression.

The Examiner has further suggested that, although the art at the time of filing taught using mice displaying phenotypes of increased anxiety or depression for screening for agents, such a utility does not reflect a use for a mouse displaying an opposite phenotype, such as those claimed. Applicants respectfully disagree. Applicants submit that the claimed mice displaying phenotypes of reduced anxiety, decreased propensity toward depression or decreased propensity toward behavioral despair would represent the ideal model of antagonism of the disrupted glucocorticoid-induced receptor gene. Therefore, such mice would provide an *in vivo* model for treating the related conditions of anxiety and depression by antagonism of the gene. These mice would be useful for a variety of applications related to drug discovery, such as, for example, determining the specificity of a putative or known agent, to compare responses of an agent in a knockout mouse and a wild-type mouse, or to determine whether putative agents would act additively or synergistically to treat disorders related to the claimed phenotypes.

The Examiner has cited Gass *et al.* (2001, *Physiology and Behavior*, Vol. 73, pages 811-825) because this reference allegedly teaches that the usefulness of mutant mice as models of depression is not clear without assessing that they specifically reflect human depression. Applicants submit that this reference is not relevant to the claimed mouse. It is standard and accepted in the art to use a variety of *in vivo* models, such as a mouse model, in the process of discovering drugs for disorders such as depression. Such an *in vivo* model is not meant to exactly mimic a human, but rather is meant to serve as a means of evaluating potential agents to narrow

down a large list of potential agents by testing whether they perform as desired in such a physiological environment. Although the claimed mice would not be considered to exactly reflect or represent human depression, they would be accepted by the skilled artisan as a valuable model useful in the evaluation and discovery of drugs for the treatment of behavioral disorders such as depression.

However, regardless of whether the claimed mice would be considered useful as a model of depression or anxiety, the transgenic mice exhibit an additional phenotype of hyperactivity. Therefore, the transgenic mice would clearly be useful for investigating agents capable of modulating or ameliorating the hyperactivity phenotype. That the mice also exhibit other phenotypes (reduced anxiety, reduced depression) does not negate the hyperactivity phenotype or the usefulness of the mice related to conditions or disorders such as hyperactivity.

Applicants believe that the rejection under 35 U.S.C. § 101 for lack of utility is improper. Applicants have asserted in the specification several specific and substantial uses for the claimed transgenic mice, described above. Further, in light of the art-recognized value of and demand for transgenic knockout mice, the asserted utilities are among many that are well-established and credible to the skilled artisan. As a result, Applicants do not believe that the Examiner has properly established that the claimed invention lacks a specific and substantial utility. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101.

**Rejection under 35 U.S.C. § 112, first paragraph**

The Examiner has also rejected claims 6, 8-10, 23, 29-32 and 35-39 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility set forth in the above utility rejection. Applicants respectfully traverse the rejection. Applicants believe that this rejection was intended to be applied to claims 36-48. Claims 42-46 have been cancelled. For the reasons set forth above in response to the utility rejection, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, has been overcome with respect to claims 36-41 and 47-48. Applicants respectfully request withdrawal of the rejection.

The Examiner has also rejected the claims under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope

with these claims. Applicants respectfully traverse this rejection. Claims 42-46 have been canceled.

Specifically, the Examiner has asserted that the specification does not enable disrupting any glucocorticoid-induced receptor gene in a mouse or any other species or a cell other than a mouse cell. Applicants have overcome this aspect of the rejection by inserting the modifier “the” before the phrase “endogenous mouse glucocorticoid-induced receptor gene” as suggested by the Examiner. Applicants have provided sufficient guidance in the specification to make and use a transgenic mouse comprising a disruption in this specific gene.

The Examiner also asserts that the specification is not enabling for a transgenic mouse of any genetic background which exhibits a phenotype of hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression. The Examiner asserts that genetic background has a significant effect on the development of the claimed phenotypes in knockout mice. Applicants submit that they have conducted their evaluation of the transgenic mice using procedures well-accepted in the art. Applicants chose to use the C57BL/6 strain to backcross because the behavior of these mice in tests such as the tail suspension test is more consistent than the behavior of other strains. This strain of mice is used widely in the art to evaluate the phenotype of knockout mice because of their consistent and predictable behavior in such tests. As a result, the skilled artisan would consider a comparison of the knockout mice to control C57BL/6 mice sufficient to determine whether the mice demonstrate a phenotype as a result of the disruption. The results, or lack thereof, for the N0 generation do not conclude that the phenotype exhibited in the N1 generation is not real. It is standard in the art to backcross to C57BL/6 mice to produce the N1 generation. This is because the N0 background may mask real phenotypes that would be revealed after such a subsequent backcross. This is likely the case for the glucocorticoid-induced receptor knockout mice of the instant invention.

The Examiner has also asserted that the method of claim 47 is not enabled by the specification because the term “murine” encompasses both mouse and rat species, while the specification has only described producing a mouse. Applicants have replaced the term murine in this claim with mouse. The specification has sufficiently described producing the claimed mouse using the method as recited in amended claim 47.

The Examiner further has alleged that claims 42-48 encompass chimeric animals. The Examiner asserts that Applicants have not demonstrated that such a chimeric animal would exhibit

the claimed phenotypes. Applicants have overcome this aspect of the rejection by reciting the phrase “whose genome comprises a disruption” such that the claimed mice encompass transgenic mice in which all somatic and germ cells comprise the disruption.

The Examiner has asserted that claims 42-48 encompass transgenic mice comprising a heterozygous disruption in the endogenous mouse glucocorticoid-induced receptor gene, but have not demonstrated that such a transgenic mouse would exhibit the claimed phenotypes, which were exhibited as a result of the homozygous disruption. Applicants have overcome this rejection by the amendment to claim 47 to recite a homozygous disruption, and by the cancellation of claims 42-46.

Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, for enablement is no longer relevant as a result of the amendment and cancellation of claims, and request withdrawal of the rejection. Claims 36-41 and 47-48 fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

The Examiner has also rejected claims 36-48 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection. Claims 42-46 have been cancelled.

In the written description rejection, the Examiner states that the specification fails to describe the DNA molecules that fall into a genus of mouse glucocorticoid-induced receptor genes as encompassed by the claims. The Examiner asserts that without the term “the” preceding “endogenous glucocorticoid-induced receptor gene” that the claims are not limiting to the mouse glucocorticoid-induced receptor gene described in the specification. Applicants have overcome the rejection by amending the claims to recite the omitted term “the” preceding the glucocorticoid-induced receptor gene. Applicants submit that the mouse glucocorticoid-induced receptor gene was sufficiently described and defined in the specification (see, for example, page 6, lines 1-11) and was known in the art (see, for example, GenBank Accession No.: M80481). As such the specification provides ample description of disruption of the claimed glucocorticoid-induced receptor gene and the phenotypes resulting therefrom.

In light of the amendment to the claims, the written description rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant. Applicants respectfully request withdrawal of the

rejection. Applicants submit that claims 36-41 and 47-48 are patentable and fully meet the requirements for written description set forth in the first paragraph of 35 U.S.C. § 112.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-359.

Respectfully submitted,

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